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The impact of age on the outcome of patients treated with radiotherapy for mucoepidermoid carcinoma (MEC) of the salivary glands in the head and neck: A 15-year single-center experience

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ABSTRACT

Introduction: Data regarding treatment and survival outcome of patients with mucoepidermoid carcinoma of the head and neck are limited to case reports and case series. As a consequence of lacking evidence, treatment guidelines do not exist. We aimed to analyze the effect of modern radiotherapy in form of intensity modulated radiotherapy (IMRT) either with simultaneously integrated boost or carbon ion boost on local control and survival for a relatively large patient collective.

Materials and methods: Patient records of 62 consecutive patients treated with postoperative (n = 53, 85%) or definitive (n = 9, 15%) radiotherapy between 2004 and 2019 were analyzed retrospectively. Kaplan-Meier estimates for overall survival (OS), distant progression-free survival (PFS), local control (LC) and locoregional control (LRC) were statistically calculated and prognostic factors were identified using the log-rank test. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE).

Results: The median follow-up was 47 months (range, 4–188 months). The 3-year OS, DPFS, LC and LRC, estimated by Kaplan-Meier curves, were 82%, 87%, 89% and 92%, the estimated 5-year OS, DPFS, LC and LRC were 78%, 87%, 84% and 88%, respectively. In univariate analysis, age > 56 years (vs. age ≤56 years) was identified as the only independent negative prognostic factor for decreased OS (HR = 1.078; 95%-CI = 1.029–1.130; $p = 0.001$), DPFS (HR = 1.055; 95%-CI = 1.000–1.114; $p = 0.051$) and LC (HR = 1.087; 95%-CI = 1.022–1.157; $p = 0.008$). Treatment was well tolerated without any grade ≥4 toxicity. Acute and late grade 3 toxicities were rare with 16% acute (n = 10) and 13% late toxicities (n = 8).

Conclusion: Radiotherapy with intensity modulated radiotherapy including either simultaneously integrated photon boost or active raster-scanning carbon ion boost for mucoepidermoid carcinomas of the head and neck

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resulted in excellent survival outcome and locoregional control with moderate toxicity. However, patients older than 56 years seem to have a disadvantage in all calculated endpoints (OS, DPFS, LRC) due to frequent local and distant relapses.

Condensed abstract: Modern radiotherapy with intensity modulated radiotherapy including either a simultaneously integrated photon boost or carbon ion boost for mucoepidermoid carcinoma results in excellent survival outcome and locoregional control with moderate toxicity. The 5-year OS, DPFS, LC and LRC, estimated by Kaplan-Meier curves, were 89%, 75%, 84% and 80%, respectively. Patients older than 56 years seem to have a disadvantage in all calculated endpoints (OS, DPFS, LRC).

Introduction

Malignant salivary gland carcinomas (MSGCs) account for 5–8% of all head and neck carcinomas and 0.4% of all tumor diagnoses [1,2]. The incidence largely depends on geography with incidence rates varying from 3% in the UK to 6–15% in Japan and the United States [3–5]. Along with adenoid cystic carcinoma and adenocarcinoma, mucoepidermoid carcinoma (MEC) belongs to one of the most common histologic subtypes with 25–35% of all MSGCs; the parotid gland representing the most common site of origin [2,6,7]. A female predominance is known for MECs with a median age at first diagnosis of 51–60 years [2].

Prognosis largely depends on tumor, node, metastasis (TNM) classification, histologic grade and primary site; parotid gland tumors having the best and submandibular gland tumors the worst prognosis [7–9]. In dependence of the tumor differentiation, the World Health Organization classification subdivides MECs into low-grade, intermediate-grade and high-grade carcinomas [10]. While 10- and 20-year survival rates of 68% and 65% are described in the current literature, these rates vary according pathologic grade with a 10- and 20-year survival of 85% and 81% for low-grade, 62% and 55% for intermediate-grade and 25% and 19% for high-grade tumors [7].

General treatment guidelines for MECs are missing. The National Comprehensive Cancer Network (NCCN) recommends surgery as first-line treatment for resectable MSGCs and requires radiotherapy in selected cases, i.e. advanced T stages, node involvement, perineural tumor invasion (PNI), incomplete resection margins and high-grade tumor differentiation. A routinely prophylactic treatment of the regional lymphatic drainage is not recommended [11,12].

The current study analyzed the impact of modern radiation treatment on local control for highly selected MEC patients who were treated either with intensity modulated radiotherapy (IMRT) alone or with a combined treatment regime with IMRT and carbon ion boost for dose-escalation (bimodal RT) in our center.

Methods

Evaluation

Sixty-two patients with pathologically diagnosed MEC who received either IMRT alone or a bimodal RT regime with IMRT and carbon ion boost between 2004 and 2019 at our center were selected for the current retrospective study. Patient records were analyzed regarding overall survival (OS), distant progression-free survival (DPFS), local control (LC) and locoregional control (LRC). In addition, prognostic factors for all four time-to-event data (OS, DPFS, LC, LRC) were assessed statistically.

Survival analysis was performed by the Kaplan-Meier method. OS was defined as time period from first diagnosis to death or last follow-up and DPFS from first diagnosis to death, distant failure or last follow-up. LC and LRC were calculated from RT start to last follow-up or local/locoregional relapse. Kaplan-Meier estimates of potential prognostic factors were compared via the log-rank test for univariate analysis with a level of significance < 0.05. All statistical tests were performed with

Table 1
Patient, tumor and treatment characteristics.

Characteristic	All patients	Patients < 56 years	Patients ≥56 years
No. of patients	62	32	30
Median age, range (y)	56, 18–88	41, 18–55	64, 56–88
Gender: male/female, n	32/30	0.19/13	0.13/17
KPS (%): 70/80/90/100, n	8/37/12/5	0.5/20/5/2	0.3/17/7/3
Smoking: yes/no, n	27/35	14/18	13/17
Tumor classification: T1/T2/T3/T4/Tx, n	9/13/20/17/3	0.6/5/11/9/1	0.3/8/9/8/2
Node classification: N 0/+/x, n	28/33/1	0.17/15/0	0.11/18/1
AJCC stage*: I/II/III/IVa/IVb/x	7/6/15/16/15/3	6/1/10/7/7/1	1/5/5/9/8/2
Metastasis classification: M0/1, n	60/2/0	0.31/1/0	0.29/1/0
Tumor differentiation: G1/2/3/x, n	26/8/22/6	0.18/3/8/3	0.8/5/14/3
PNI: yes/no/unknown, n	13/47/2	0.6/26/0	0.7/21/2
LVI: yes/no/unknown, n	11/49/2	0.6/26/0	0.5/23/2
Tumor site: minor/major salivary gland, n	23/39	0.10/22	0.13/17
RT setting: postoperative/definitive, n	53/9	30/2	23/7
Total/partial resection of the parotid gland	17/5	10/3	7/2
Total/partial resection of the submandibular gland	15/0	7/0	8/0
Total/partial resection of the sublingual gland	2/0	2/0	0/0
Resection margin: R0/R1/R2, n	24/18/11	13/8/7/4	11/10/8
IMRT alone, n	11	4	7
Median total dose, EQD2	66 Gy	66 Gy	66 Gy
Range total dose, EQD2	60–70.4 Gy	66–70.4 Gy	60–70.4 Gy
IMRT + C12 boost, n	51	28	23
Median total dose, EQD2	78 Gy	80 Gy	78 Gy
Range total dose, EQD2	68–86 Gy	74–86 Gy	68–86 Gy
Concomitant Cisplatin weekly, n	15	10	5

Abbreviation: KPS = Karnofsky Performance Score, TNM = tumor, node, metastasis, G = grading, PNI = perineural invasion, LVI = lymphovascular invasion, EQD2 = equivalent dose to 2 Gy fractions, C12 = carbon ions, n = number. *8th edition.

SPSS Statistics version 24 (IBM, Armonk, New York, USA) and R version 3.4.2. (www.r-project.org).

Follow-up and toxicity

Regular follow-up examinations every three months during the first two years after RT, every half year during the next two years and then, once a year including a clinical examination by a head and neck surgeon and a magnetic resonance imaging (MRI) were performed. A computed tomography of the chest and the upper abdominal organs was required annually. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [13,14]. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE). Acute toxicity was defined as toxicity which was reported under RT and latest three months after completion of RT and chronic toxicity as toxicity which occurred ≥3 months after RT.

Patient characteristics

The median age of our patient collective was 56 years (range, 18–88 years). The patient and tumor characteristics for the whole patient population, for patients ≤56 years and > 56 years are shown in Table 1. In Fig. 1, we demonstrate the age distribution at first diagnosis via quartiles. Overall, a quarter of patients developed a MEC between an age of 56 and 64 years with a peak at 58 years.

Treatment characteristics

A native CT in irradiation position with a custom-made thermoplastic head mask and shoulder fixation was performed for target delineation. A contrast-enhanced CT and MRI were matched to the native planning CT for tumor demarcation. Clinical target volume 1 (CTV1) including the macroscopic tumor (gross tumor volume, GTV) or tumor bed after surgery and CTV2 including CTV1, potential locoregional pathways of tumor spread and the prophylactic neck were outlined. For the planning target volume (PTV), a 3 mm margin was added to the CTV. Target volumes were large with 138 ccm for CTV1 (range 35–484 ccm) and 325 ccm for CTV2 (range 98–875 ccm). IMRT plans were created by using TomoTherapy® platform and carbon ion plans using Siemens TPS® according to the local effect model (LEM) [15].

IMRT was applied by TomoTherapy® in 5 fractions per week and carbon ions by active beam technique with intensity-controlled rasterscanning in 5–6 fractions a week. The median PTV was at least covered by 95% of the prescribed isodose. Normal tissue was spared according to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data as low as possible [16]. For improved comparability, the equivalent dose in 2 Gy per fraction was calculated using the formula $EQD2 = D \times ((d + \alpha/\beta)/(2 + \alpha/\beta))$ (D = total dose in Gy; d = fraction dose in Gy; $\alpha/\beta = 2$). All patients received an IMRT base plan to the CTV2 with simultaneously integrated IMRT boost (n = 11, 18%, median equivalent dose to 2 Gy (EQD2) of 66 Gy, range 60–70.4 Gy) or carbon ion boost (n = 51, 82%, median EQD2 of 78 Gy, range 68–86 Gy) to the CTV1. Due to its physical and biological advantages, significantly higher doses could be applied with carbon ion RT compared to IMRT (Fig. 2). For detailed treatment characteristics, please see Table 1.

Results

Survival analysis and prognostic factors

The median follow-up was 47 months (range, 4–188 months). At last follow-up, 81% of the patients were still alive (n = 50). Overall, a local recurrence was diagnosed in 11% (n = 7) of the cases within a median time of 20 months after RT (range, 7–106 months), a locoregional recurrence in 18% (n = 11) within a median time of 21 months after RT (range, 5–106 months) and distant recurrence in 13% (n = 8) of the patients (lung n = 4, bone n = 2, both bone and lung n = 1, brain n = 1) within a median time of 12 months after first diagnosis (range, 4–22 months). The 3-year OS, DPFS, LC and LRC, estimated by Kaplan-Meier curves (Fig. 3), were 82%, 87%, 89% and 92%; the estimated 5-year OS, DPFS, LC and LRC were 78%, 87%, 84% and 88%, respectively. In univariate analysis, tested for age (> vs. ≤56 years; median age was 56 years), Karnofsky performance score (90–100% vs. 70–80%), smoking (yes vs. no), minor vs. major salivary glands, TNM stage (T1-3 vs. T4; N0 vs. N+), G stage (G1-2 vs. G3), PNI (pos. vs. neg.), EQD2 (< 70 Gy vs. ≥70 Gy), primary vs. postoperative RT, IMRT alone vs. bimodal RT and resection margin (R0 vs. R1 vs. R2) as valuable prognostic factors, age > 56 years was identified as the only independent negative prognostic factor for decreased OS (HR = 1.078; 95%-CI = 1.029–1.130; $p = 0.001$), DPFS (HR = 1.055; 95%-CI = 1.000–1.114; $p = 0.051$) and LC (HR = 1.087; 95%-CI = 1.022–1.157; $p = 0.008$; supplementary table 1, Fig. 4).

Acute and late toxicities

No acute grade ≥4 toxicities were observed. Acute grade 3 toxicities occurred in overall 10 patients (16%), while the most reported acute grade 3 toxicities were mucositis (n = 4, 6%), dermatitis (n = 2, 3%) and xerostomia (n = 2, 3%). Regarding late grade 3 toxicities, the majority of patients claimed xerostomia (n = 3, 5%), trismus (n = 2, 3%) and hearing impairment (n = 2, 3%). Overall, 8 patients claimed late grade 3 adverse side effects (13%). Brain injury was diagnosed in only 1 patient (2%) 14 months after RT. Due to headache and increasing dizziness, the patient was treated with oral cortisone treatment (grade 2). Symptoms disappeared completely one week after treatment start. Osteoradionecrosis of the mandibular bone (n = 1, 2%) was diagnosed 8 months after RT in one patient with MEC of the parotid gland who was irradiated with an EQD2 of 80 Gy via bimodal RT. In another patient with MEC of the minor salivary glands in the nasopharynx who was irradiated with IMRT alone at an EQD2 of 70.4 Gy osteoradionecrosis of the temporal bone (n = 1, 2%) occurred 28 months after RT. They were managed with conservative treatment methods, i.e. cortisone treatment in one case (grade 2, 2%) and surgery was necessary in another case (grade 3, 2%). Acute hearing impairment was assessed in 2 patients (3%) and increased during follow-up. At last follow-up, 5 patients (8%) claimed hearing impairment of whom 2 patients received concomitant cisplatin weekly chemotherapy (3%). Only one patient with MEC of the parotid gland who was irradiated with an EQD2 of 86 Gy via bimodal RT needed a hearing device due to severe hearing loss (grade 3; 2%). Visual impairment was relatively rare. Grade 2 acute visual impairment occurred in 3 patients (5%) and grade 2 late visual impairment in 2 patients (3%). In all five cases, visual impairment was caused by keratoconjunctivitis (8%). Acute and late

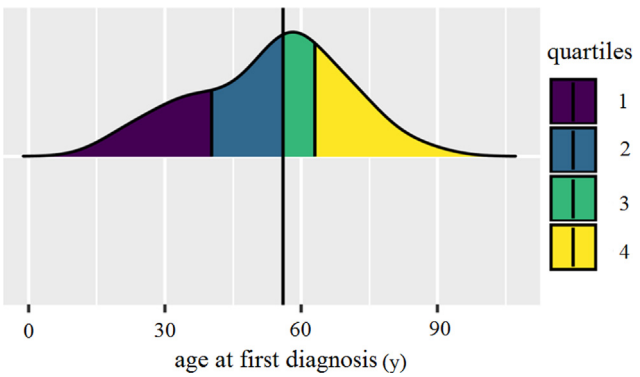

Fig. 1. Age distribution (at first diagnosis). Overall, a quarter of patients developed a MEC between an age of 56 and 64 years with a peak at 58 years.

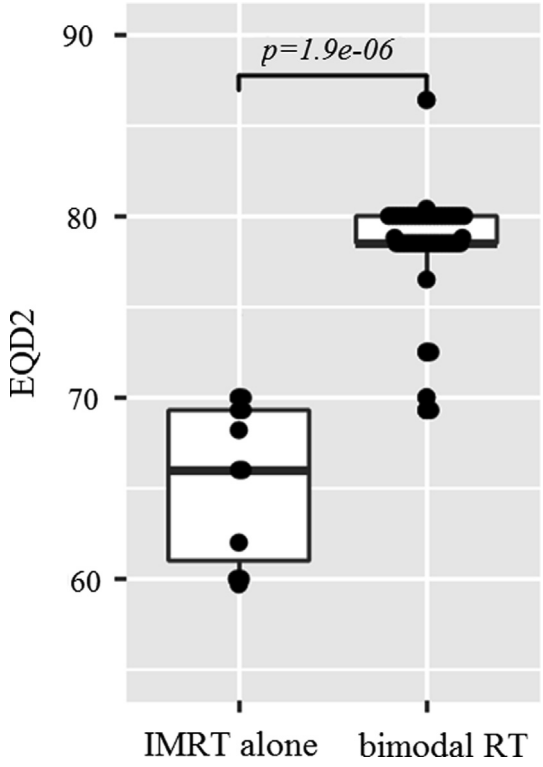

Fig. 2. Dose distribution in equivalent dose to 2 Gy fractions (EQD2) between the two radiotherapy groups of IMRT alone and bimodal RT (IMRT base plan + carbon ion boost). With bimodal RT, significantly higher doses could be prescribed to the tumor ($p < 0.001$).

adverse events grade ≥2 are shown in Table 2.

Discussion

The majority of patients in the current study was treated postoperatively (85%) and only 15% were irradiated definitely due to inoperability of the tumor (n = 9/62). Despite unfavorable patient characteristics, excellent OS, DPFS, LC and LRC rates with a 3-year OS, DPFS, LC and LRC of 82%, 87%, 89% and 92% were achieved with modern RT techniques (IMRT alone and IMRT + C12). Age was identified as the only prognostic factor for OS, DPFS and LC; patients > 56 years having a survival disadvantage in all three endpoints. Although the majority of our patients received dose-escalated RT > 70 Gy (82%), toxicity was low with only 16% acute and 13% late grade 3 toxicity.

Surgery represents the mainstay of treatment in MSGCs and definitive RT is reserved for patients with inoperable tumors. In highly selected patients with unfavorable characteristics known for decreased local control after surgery, i.e. close margins, gross residual disease, high-grade differentiation, advanced T stage (T3-4), nodal involvement and the presence of perineural invasion (PNI), RT is recommended postoperatively [17]. The beneficial effect of additive RT to surgery is still shown in several studies [18]. The Dutch Head and Neck Oncology Cooperative Group reported a significant increase in the 10-year LC rate from 18% to 84% in T3-4 tumors, from 44% to 82% in gross residual tumors, from 55% to 95% in case of close margins, from 60% to 88% for PNI and from 62% to 86% for N+ by postoperative RT compared to surgery alone [19,20]. In addition, Al-Mamgani et al. could show excellent survival outcome for MEC patients after surgery and postoperative photon RT with an event-free survival at a median follow-up of 58 months of 78% and locoregional failure of 19% [21].

For MECs as well, postoperative RT seems to increase local control in high-risk patients. While Chen et al. could show in a retrospective research of 207 patients including 67 MEC patients 10-year locoregional control rates of 37% to 63% after surgery alone, locoregional control after postoperative RT, predominantly based on studies which considered MEC as one among several other histologies of MSGCs, ranged between 76% and 84% [22–24]. For patients who were treated either with photon or mixed photon and electron beam RT with a median total dose of 60 Gy (range 45–70 Gy) postoperatively, Chen et al. and Park et al. reported a 5-year local control of 84% and 91%, significantly depending on T stage (T1: 92%; T2/3: 83; T4: 64%), tumor location (parotid vs. non-parotid) and N stage (N0/1 vs. N2) [24,25]. Hosokawa et al. showed equal LC and survival rates with a 5- and 10-year LC of 89% and 80% and OS of 73% and 63% for patients treated with postoperative photon RT ≥55 Gy vs. surgery alone although positive margins were more frequently diagnosed in the postoperative RT group [26]. Salgado et al. reported a 5-year LC of 78% for MECs treated with postoperative photon RT with a median dose of 63 Gy [27]. In the current study, a 3-year LC rate of even 89% could be achieved while the majority of our study collective was irradiated postoperatively (n = 53/62; 85%).

In univariate analysis, there was no statistically difference in the survival outcome of postoperatively vs. definitely irradiated patients. The role of definitive RT in the treatment of inoperable MECs is still unclear. Some authors report LC rates between 48% and 58% for MSGCs treated with definitive photon beam RT up to doses of 66–70 Gy [19,28]. The NCCN recommends doses between 60 Gy and 66 Gy in the postoperative setting and at least 66 Gy in the primary setting for MSGCs. Nevertheless, higher doses are necessary for sufficient tumor control as multiple studies showed a dose-dependence regarding tumor response [12,18].

The development of more conformal RT techniques and especially of high-linear energy transfer RT with neutrons and carbon ions enabled the delivery of higher biological effective doses on the target and resulted in an increase of local control in MSGCs [29–31]. For MECs, Jensen et al. reported a 3-year LC of 70% for high-risk patients who received either postoperative or definitive RT due to the inoperability of the tumor including IMRT and carbon ion boost up to equivalent doses to 2 Gy fractions of 80 Gy [11]. The Japan Carbon Ion Radiation Oncology Study Group could achieve in a multi-institutional retrospective study a 3-year LC and OS rate of even 95% and 89% by definitive carbon ion radiotherapy up to 64 Gy (RBE) in 16 fractions for MECs [32,33]. In the current study, we achieved a lower 3-year LC and OS rate of 89% and 82% compared to the Japanese data, possibly substantiated by patient selection bias.

The impact of RT on OS in MSGC and especially in MEC patients still remains unclear and is discussed controversially by several authors. While some authors could identify a positive impact of postoperative RT on survival in squamous cell carcinoma patients only, others reported a survival advantage for postoperative RT in patients with tumors located in the parotid gland, of high-grade differentiation, advanced T and N stage and adenoid cystic histology [34–36].

For MEC, tumor differentiation is known as the strongest prognostic factor for overall and disease-specific survival regardless of treatment modality, so that the WHO classifies MECs into three prognostic groups; low-grade, intermediate-grade and high-grade [9,10]. Thus, 5-year survival rates of 75–99% for low-grade, 80–97% for intermediate-grade and 23–52% for high-grade MEC are reported in the literature [7,9,12,24,37]. Tumor differentiation does not only influence survival, but also impacts nodal and distant failure as well as the aggressiveness of metastases [9,12,38–41]. Chen et al. showed a nodal failure into ≥1 regional neck nodes of 4% for low-grade, 9% for intermediate-grade and 43% for high-grade MECs [9]. In the current study, overall 53% of the patients showed lymph node metastases initially (n = 33/62), considerably more than prescribed in the current literature. Nevertheless, RT with modern techniques resulted in an excellent LRC rate with a 3-year LRC of 92%. Rapidis et al. and Brandwein et al. reported as well, that nodal and distant metastases occurred more frequently in

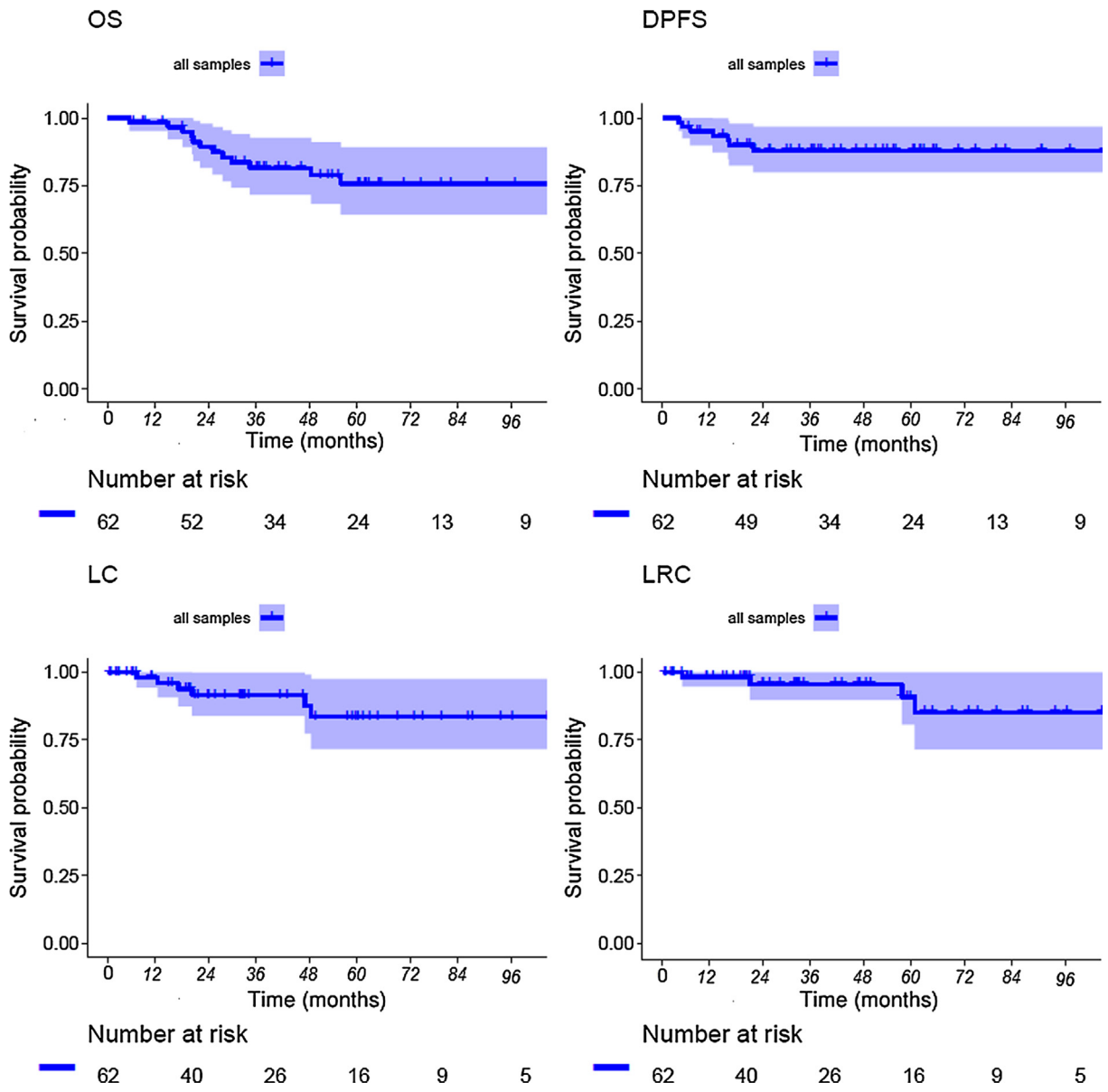

Fig. 3. Kaplan-Meier estimates for overall survival (OS), distant progression-free survival (DPFS), local control (LC) and locoregional control (LRC) for the whole cohort.

high-grade and locally advanced tumors, while metastases of high-grade tumors lead significantly more often to deaths than metastases of low-grade tumors. Average survival for high-grade MEC patients after first diagnosis of distant metastases was 2.3–2.6 years in the mentioned studies [38,39]. These findings could be strengthened by other authors as well [27]. In conclusion, the management of local failure, especially in high-grade MEC, is essential for cure and therefore, dose-escalating radiation methods, e.g. with carbon ion boost, and the neck irradiation for locoregional control should be individually discussed. Besides tumor differentiation, several other factors, i.e. age, tumor location, tumor size, distant metastases and nodal involvement, affect nodal and distant failure and consequently survival significantly [8,24,37,38,40]. Guzzo et al. identified decreased disease-free survival for MECS located in the minor salivary glands vs. major salivary glands with a 5-year disease-free survival of 80% for low-grade MEC of the minor vs. 97% for low-grade MEC of the major salivary glands [37]. In the current study, treatment setting (definitive vs. postoperative RT), tumor differentiation (G1/2 vs. G3), tumor site (minor vs. major salivary glands) and treatment dose had no significant impact on OS, LC and LRC. In the current analysis, smoking could not be identified to have an impact on the outcome of our patient collective. Sawabe et al. as well could not identify a correlation between smoking and the prevalence of MEC by comparing MEC patients with a control group without cancer [42]. Age at first diagnosis was identified as the only factor having prognostic relevance regarding OS, DPFS and LRC. Thus, MECs in older patients seem to be more aggressive which may be explained by immunological processes [43]. Overall, metastasis-free survival rates between 70% and 78% were reported in the literature [24,27,40].

Based on these findings, high-grade MECs in locally advanced stages should be treated more aggressively due to frequent nodal and distant metastases, influencing survival much more negatively than local failure. Especially for high-grade MECs, a routine treatment of the clinical negative neck either in form of surgical neck dissection or prophylactic neck irradiation and systemic approaches (in form of concomitant chemotherapy to radiation) to prevent or treat distant failure in order to improve survival should be considered. The current evidence concerning both elective treatment of the neck and systemic treatment options for MEC is unclear due to the rarity of the disease and

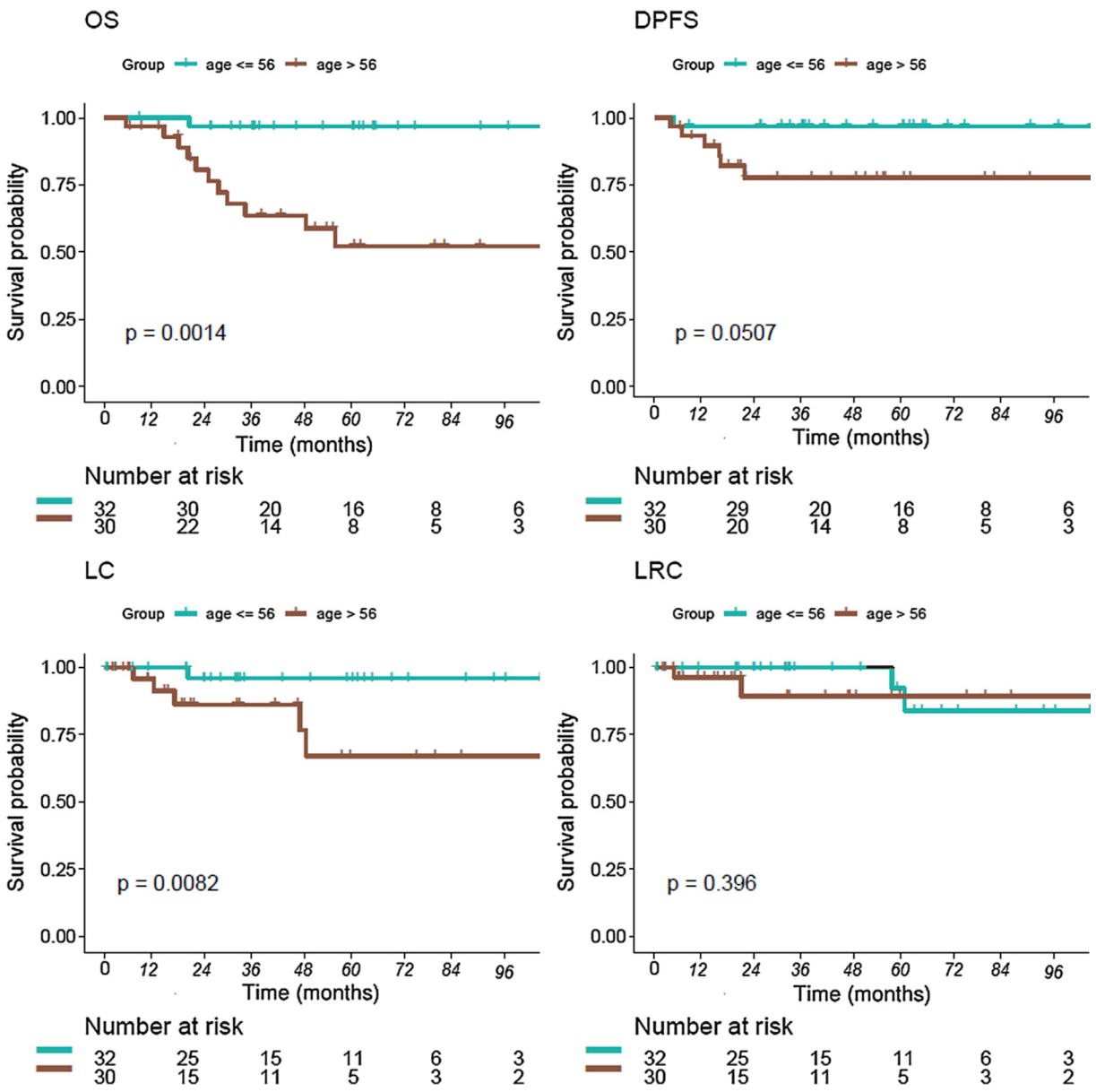

Fig. 4. Kaplan-Meier estimates for overall survival (OS), distant progression-free survival (DPFS), local control (LC) and locoregional control (LRC) in dependence of age ≤56 vs. > 56 years. Patients > 56 years showed a significant worse OS ($p = 0.001$), DPFS ($p = 0.051$) and LC ($p = 0.008$).

a lack of randomized studies. Nevertheless, few retrospective data show a high sensitivity of MEC to different kinds of chemotherapy regimens including cisplatin, doxorubicin and taxol in small patient series [44–46]. In the current study, only 24% received concomitant Cisplatin weekly radiotherapy, which is not sufficiently high enough to explain the favorable results in the current study (n = 15/62). Besides the limited patient number, further factors, i.e. the retrospective design of the current study and patient selection bias, make the interpretation of our results difficult and should be taken into account before making a clear conclusion.

Although higher biological effective doses were prescribed to the target with a combination treatment schedule including IMRT and carbon ion boost in the majority of cases, toxicity rates were moderate and comparable to those after photon RT. The most frequently reported acute grade 3 toxicities were mucositis, dermatitis and dysphagia. Salgado et al. reported 20% acute grade 3 toxicities after photon RT predominantly consisting of mucositis and dysphagia [27]. For bimodal RT consisting of IMRT and carbon ion boost, Jensen et al. reported 15% acute grade 3 side effects including mucositis, dermatitis and dysphagia [11]. In previously published studies, we could show a similar toxicity profile for bimodal radiotherapy regarding several tumor locations, i.e. nasopharyngeal carcinomas, laryngeal carcinomas, lacrimal gland carcinomas and carcinomas of the oral cavity, consisting of 10% to 23% grade 3 toxicities [47–50]. For exclusive carbon ion RT, 19% acute grade 3 mucositis and 8% acute grade 3 dermatitis were reported by Shirai et al. [32]. Regarding severe late toxicities as well, similar toxicity rates with differing toxicity profiles could be identified for photon and carbon ion RT. While for photon RT 11% late grade 3 toxicities with severe late dysphagia (3%), xerostomia (3%), trismus (1%) and hearing loss (4%) were observed, this rate was 15% for bimodal RT consisting of hearing impairment (13%) and tissue necrosis (2%) and 14% for exclusive carbon ion RT including brain injury (4%) and osteonecrosis of the jaw (11%) [11,27,32]. Especially xerostomia seem to be a major side effect decreasing the quality of life of patients with salivary gland tumors [21,51]. Several authors described a dependence of surgery and RT technique and the occurrence of acute and late xerostomia [51,52]. Van Luijk et al. showed that the function of the parotid gland could be preserved after radiotherapy by sparing parts of

Table 2
Acute and late adverse events (grade ≥ 2).

	Acute grade ≥ 2, No. (%)			Late grade ≥ 2, No. (%)		
	Grade 2	Grade 3	Total	Grade 2	Grade 3	Total
Mucositis	19 (31)	4 (6)	23 (37)	1 (2)	0	1 (2)
Dermatitis	13 (21)	2 (3)	15 (24)	0	0	0
Xerostomia	7 (11)	2 (3)	9 (14)	6 (10)	3 (5)	9 (15)
Dysphagia	21 (34)	7 (11)	28 (45)	3 (5)	0	3 (5)
Dysgeusia	10 (16)	0	10 (16)	3 (5)	0	3 (5)
Dysosmia	6 (10)	0	6 (10)	4 (6)	0	4 (6)
Trismus	3 (5)	0	3 (5)	4 (6)	2 (3)	6 (10)
Neuropathic pain	1 (2)	1 (2)	2 (3)	1 (2)	0	1 (2)
Visual impairment	3 (5)	0	3 (5)	2 (3)	0	2 (3)
Due to keratoconjunctivitis	3 (5)	0	3 (5)	2 (3)	0	2 (3)
Hearing impairment	1 (2)	1 (2)	2 (3)	3 (5)	2 (3)	5 (8)
Due to tympanic effusion	1 (2)	1 (2)	2 (3)	2 (3)	1 (2)	3 (5)
Brain injury	0	0	0	1 (2)	0	1 (2)
Osteonecrosis	0	0	0	1 (2)	1 (2)	2 (3)
Maxillary bone	0	0	0	1 (2)	0	1 (2)
Temporal bone	0	0	0	0	1 (2)	1 (2)
Cranial nerve dysfunction*	1 (2)	0	1 (2)	2 (3)	0	2 (3)
Facial nerve	1 (2)	0	1 (2)	1 (2)	0	1 (2)
Trigeminal nerve	0	0	0	1 (2)	0	1 (2)

Abbreviations: none.
* Only rt-induced cases.

the gland which contain the major ducts [51]. In the current study, the majority of patients who were irradiated postoperatively received a total resection of the salivary gland. In addition, no salivary gland sparing methods were applied during RT. Nevertheless, the xerostomia rate was relatively low comparing with data in the literature, possibly due to the high rate of patients treated with carbon ions and patient selection bias (not only parotid gland tumors in the current study, but also minor salivary gland tumors, 15% vs. 40%) [51]. Concerning brain injury and osteonecrosis, several authors identified a dose-dependence while significantly more brain injuries and osteonecrosis occurred at RT doses > 70 Gy which can possibly explain the predominant occurrence of these symptoms after high linear energy transfer RT [53–61]. Although high doses (median total EQD2 of 80 Gy) were applied in the current study, only one case of brain barrier disruption (2%) and two cases of osteonecrosis (3%) occurred in the current study.

Conclusion

Radiotherapy with intensity modulated radiotherapy including either simultaneously integrated photon boost or active raster-scanning carbon ion boost for mucoepidermoid carcinomas of the minor and major salivary glands of the head and neck resulted in favorable survival outcome and locoregional control with moderate toxicity. However, patients older than 56 years seem to locally relapse and metastasize more frequently affecting all calculated endpoints, i.e. OS, DPFS, LRC, negatively.

Ethics approval and consent to participate

The final protocol was approved by the ethics committee of the University Heidelberg, Germany and accepted on 03/14/2017 (acceptance number: S-421/2015).

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during the current study are included in this published article. The dataset is available from the corresponding author on reasonable request.

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Author contribution

Conceptualization, S.Ak, AH and SA; methodology, S.Ak and SA; formal analysis, S.Ak; writing—original draft preparation, S.Ak.; writing—review and editing, AH, AM, S.Ak. SA, TH, KL, JH, TF, SK, S.Ka., KH, PP, SR, JD, and SA*; supervision, SR, KH, JD and SA

Declaration of Competing Interest

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Appendix A. Supplementary material

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